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Virtual Pharmaceutical Companies: collaborating flexibly in Pharmaceutical Development

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Virtual companies; Pharmaceutical R&D; Collaboration; Strategy; R&D Pipeline; Business models

Big pharmaceutical companies can beneficially leverage the virtual company concept as one way to tackle today's industry challenges by choosing appropriate modes of collaboration described herein.

Abstract: R&D collaborations represent one approach chosen by the pharmaceutical industry to tackle today's challenges posed by declining internal R&D success rates and fading of the blockbuster model. In recent years a flexible concept to collaborate in R&D has emerged: virtual pharmaceutical companies (VPCs). They differ from other R&D companies, e.g. biotech start-ups, collaborating with big pharmaceutical companies, as VPCs consist solely of experienced teams of managers. VPCs have only been described anecdotally in literature. Herein, we present the characteristics of a VPC and suggest how big pharma can leverage the concept of VPCs by introducing five possible modes of collaboration. We find that one mode – investing – is particularly promising for big pharma.

Today's challenges for the pharmaceutical industry are well documented: declining internal R&D success rates coupled with patent expiries of important cash-generating drugs, governments pursuing austerity policies, regulatory agencies tightening their demands, and drugs failing in late stages of development in times of rising overall R&D costs [1–5]. The golden era of the blockbuster business model in the pharmaceutical industry seems to be past. Nevertheless, pharmaceutical companies have tried to peg to their model by undergoing several rounds of mergers and acquisitions (M&As) to bolster their R&D pipelines, further leading to advantages in marketing and the conduct of clinical trials. In R&D, however, size does not necessarily translate into higher output, as the thus created R&D silos often disrupt creativity and initiative [1,6,7]. A further hindrance to increased innovation lies in the closed IP system, on which the business model of the pharmaceutical industry is based, which impedes beneficial knowledge sharing.

The past years were marked by intense restructuring efforts by pharmaceutical companies – not only after M&As: organizational changes and new approaches to research are hoped to reduce development cycle times, late-stage failures, costs and complexity [8,9]. As alternatives to M&As, outsourcing to contract research organizations and collaboration with academia, suppliers and

other drug development companies have gained attention as means to tackle the problem of decreasing R&D success rates and empty development pipelines [10–15]. Outsourcing and collaboration bear the potential to redistribute risks, streamline R&D, fill the pipeline and to extend capacities. Furthermore, the associated reduction in internal headcounts and fixed costs mitigates the impact of failures in pre-clinical, phase I & II clinical trials.

It is further suggested that the industry should evaluate more radical approaches to modify its business model [5]. Extreme forms of outsourcing and collaboration, for instance, are represented by virtual pharmaceutical companies (VPCs). VPCs emerged in the 1990s, with Roche's Protodigm Ltd as the first example of a big pharma founding of a VPC, and are now a known part of the pharmaceutical industry [16]. In the literature, VPCs have been described anecdotally [17–19], including a recent presentation of a model to determine whether a company is virtual or not [20], but a more general perspective regarding big pharma – VPC collaborations is lacking. In the present paper we therefore provide deeper insights by describing the concept of a virtual company in the context of the pharmaceutical industry. Most importantly, we suggest how big pharma can leverage VPCs by presenting five possible modes of collaboration and their respective advantages and pitfalls.

What are Virtual Companies?

In current literature, a virtual company is described as either being an alliance network, a partly-disintegrated firm or a company that outsources everything. In the context of the pharmaceutical industry and the present paper, we define true VPCs as the most radical of these three forms: a VPC consists of a small management and consulting core, which coordinates and monitors on a contractual basis a set of service providers to perform all operational activities to develop one or several drug candidates [16,21]. Depending on the respective business models, these candidates for instance stem from the founders' past academic research or from big pharmaceutical companies, as will be discussed below. The goal of a VPC is to reach fast Proof of Concept (PoC) at modest cost, which is enabled by the lack of expensive corporate infrastructure

to be used for the project and by foregoing activities, such as synthesis optimization, which are unnecessary for the demonstration of PoC (Figure 1) [19]. The term *virtual* refers to the business model of such a company based on the managerial core, which coordinates all activities with external providers, and on the lack of internal production or development facilities rather than to the usage of the internet or electronic communication. Any service provider available on the market can be chosen for a project, as almost no internal investments in fixed assets are made. In most cases, the focus of VPCs lies solely on development activities rather than on the commercialization of drugs (registration, large-scale manufacturing, marketing, supply chain and pharmacovigilance), which is preferably carried out by big pharma due to the high costs and resource requirements involved. Importantly, VPCs differ from small biotech start-ups, as the latter still retain their own in-house R&D laboratories and other functions.

[approximate location of figure 1]

The main advantages of VPCs consist in their development speed and efficiency due to their fast-to-PoC strategy, as well as in their flexibility to choose the most suitable resources and contractors for every specific development step of a project and in the absence of expensive fixed assets leading to low overhead costs [16]. The VPC model thus enables scientists and entrepreneurs with limited access to capital to found a company for the development of their compounds. In particular, the foundation of academic spin-off companies in the form of VPCs could be attractive. Intensive outsourcing further allows VPCs to focus on their core competences in the product-related scientific field, in managing IP and in coordinating their relationships to and their work with external service providers, creating an environment for fast and rigorous decision making. On the other hand, the total dependence on external service providers also represents one of the major drawbacks of VPCs [21]. The development of the drug is at risk, if a contractor fails to deliver the specified quality of services or even gets into financial distress. Contracts should therefore include provisions for premature termination. However, the large number of service providers in the market allows the selection of financially stable partners with a proven track record or – should issues arise – to switch to a different

company taking into account possible switching costs. Reduced security and confidentiality as well as possible information deficits towards the external contractors have also been mentioned as disadvantages of VPCs. As the number of contacts to external providers increases, so does the risk to lose critical information, especially when contractors work for competitors as well. Sufficient attention, planning and security provisions, e.g. by concentrating the project-specific in-depth knowledge in the VPC's management core, however, can minimize the risks. Lastly, interactions between different suppliers present a real challenge for managers of VPCs, as they might lead to confusion and time delays if not appropriately coordinated.

All these points suggest that the know-how and abilities of the members of the core management team are central to a VPC's success, as they are the only ones having the full in-depth knowledge concerning the project. The managers must possess strong industrial and academic networks, be decisive and unafraid to pull the plug on unpromising projects. They further need extensive expertise in drug development and clinical trial conduction, proven leadership and project management skills, entrepreneurial spirit and proficiency in handling suppliers. Of course, the critical dependency on the skills of every single team member leaves little room for mistakes as well as incompetency, and the survival of a VPC might be endangered if one of its core members resigns unexpectedly.

Even in case of excellent performance a VPC should remain small to preserve its advantages of efficiency and low fixed costs. Still, success depends on the efficacy and toxicology profile of the drug under development. Nevertheless, the contracts of VPCs with their external providers are normally rather short term and thus allow for easier reallocation of resources from a failed project to the next promising candidate.

Considering the aspects discussed above, VPCs merit their existence in the landscape of the pharmaceutical industry in their own right. In the next section, however, we examine how big pharma could leverage the concept of VPCs as one strategy to tackle the industry's challenges

mentioned in the beginning. Thereby we present five possible modes of collaboration between big pharma and VPCs.

Five possible modes of collaboration between big pharma and VPCs

As big pharmaceutical companies increasingly look for opportunities to collaborate in R&D, we suggest VPCs as novel additions to their existing portfolio. At first sight, some of the five modes of collaboration between big pharma and VPCs we have identified – *In-licensing, Founding, Buying, Investing* and *Out-licensing* (Figure 2) – seem to be well-known from other partnerships in the industry. However, the innovative business model of VPCs, for which integrated pharmaceutical companies are too big, offers specific opportunities and advantages. In our description of the five modes below, we therefore highlight unique elements in collaborations between pharmaceutical companies and VPCs where present.

[approximate location of Figure 2]

MODE 1: In-licensing

Of the five modes, in-licensing agreements with VPCs are most similar to existing collaborations between big pharma and e.g. biotech or small pharmaceutical companies. Benefits for big pharma hereby lie mainly in the specific advantages of VPCs compared to other R&D companies, such as their fast-to-PoC strategy and their cost efficiency. From a VPC's perspective, licensing agreements represent convenient exit strategies. They ensure continuous cash flows, provide means to circumvent the lack of resources for late stage development and enable financing of future development projects. Examples for VPC applying this business model include ReGen (www.regentherapeutics.com), Provectus pharmaceuticals (www.pvct.com) and GenSpera (www.genspera.com), which are funded by private investors, federal grants and by the issuing of common stock.

Basic licensing deals between pharmaceutical companies and VPCs comprise an exchange of IP against a single payment. However, competition amongst big pharmaceutical companies for

targets having passed PoC is high and so are the required investment sums. More favorable are thus early-stage deals that include, besides an up-front payment, several success-dependent milestone payments to in combination with royalties upon commercialization. This approach requires significantly less investments than a late-stage entry, concomitantly mitigating the risk associated with compounds in early development.

MODE 2: Founding

The second mode of collaboration describes a pharmaceutical company founding its own virtual subsidiary. In this case, the subsidiary is a judicial limited company which uses the virtual concept to develop specific products of its parent company with external resources until PoC. Although the compounds for development are given by the parent company, an "entrepreneurial owner spirit" might arise among the few executives as they independently manage and decide on the development partners [22]. One example for a company applying this collaboration mode is Eli Lilly, who founded its virtual subsidiary Chorus in 2002. According to Chorus' employees Roberson, Smith and Scherer, this approach allows Eli Lilly to "pursue many more leads at a fraction of the time and cost" usually required [22]. The rigorous selection process followed by the managers of the VPC ensures that only candidates with a high probability of technical success advance to late stage development within the parent company. "Although Chorus absorbs just one-tenth of Lilly's investment in early-stage development, it has recently delivered a substantially greater fraction of the molecules slated for late Phase II trials – at almost twice the speed and less than a third of the cost of the standard process […]" [19]. Furthermore, Chorus leverages the possibilities presented by sophisticated IT tools to increase the efficiency of its development activities [22]. Another example for a VPC falling into this category is Protodigm Ltd, which was introduced before. After its parent Roche decided to close the company, it was transformed into the independent company Fulcrum Pharma Developments Ltd and later merged with other companies to create a CRO named Aptiv Solutions [16].

By founding their own VPC, pharmaceutical firms can easily harness both integrated, "secure" R&D and efficient exploitation of external resources. They can minimize risks, costs and time for drug development, concomitantly profiting from a business model unlike their own. To ensure success, the parent company needs to set clear objectives, yet support independent and fast decision making within the VPC.

MODE 3: Acquiring

Acquisitions – today a widely selected procedure in the pharmaceutical industry – represent the third model of big pharma – VPC relationships. Traditional, large M&A deals within the pharmaceutical industry generally require extensive integration efforts and thereby negatively influence R&D as well as employee productivity [23]. When acquiring a VPC on the other hand, the vendee solely buys IP, the product and possibly the skilled management core avoiding the negative consequences of traditional deals with biotech or small pharmaceutical companies. With its 2005 acquisition of Angiosyn, which had one compound in pre-clinical development, Pfizer is just one example for a big pharma company in this category.

However, to fully leverage the advantages of a VPC acquisition, pharmaceutical companies need to consider the structure as well as the timing of the deal. Especially for early-stage acquisitions, payments by big pharma should be success-dependent and based upon the completion of several milestones such as regulatory approvals. Regarding the timing of the take-over, big pharmaceutical companies must wait until the VPC developed the target to PoC, as otherwise the efficiency of the virtual model is diminished or lost in the more bureaucratic environment of the parent company. The pharmaceutical company would have to coordinate mixed development teams with potentially different cultural backgrounds and business perceptions, which likely complicates and decelerates the drug development process.

MODE 4: Investing

The forth relationship model consists of an investment deal, with a big pharma venture fund assuming the role of the investor. Almost every large pharmaceutical company governs its own

venture fund[1] and Bruce Booth from Atlas Ventures reported that from 2009 to 2012, 67% of their Life Sciences deals included at least one corporate venture fund (see: http://lifescivc.com/2012/01/corporate-pharma-vcs-preferred-partners-big-funds/). [2] The average pharma venture fund size is approximately US$250 million with an average annual investment volume of around US$20 million. Considering the cost efficiency of VPCs, a significantly higher number of virtual than integrated companies can be funded with a given investment sum. Pharma venture funds that balance investments into start-ups, small biotech *and* VPCs, can thus establish an even more diversified portfolio and at the same time ensure to keep pace with new technologies and business models. The VPC Flexion, for instance, was founded in 2007 by executives, who led Eli Lilly's Chorus before. Pfizer's Venture Capital group alone contributed $9 million to Flexion's Series A financing, which closed at $42 million (www.flexiontherapeutics.com), and thus Pfizer, as investor, receives detailed information about the company and its pipeline.

MODE 5: Out-licensing

As big pharmaceutical companies streamline their R&D strategies, many compounds outside their therapeutic focus areas are not further developed [24]. These compounds can be out-licensed to VPCs for development according to their cost-efficient fast-to-PoC strategy. In contrast to out-licensing deals with other pharmaceutical companies, agreements with VPCs might include an option for the licensee to re-in-license the formerly out-licensed compound after PoC is achieved. Alternatively, VPCs might be asked to process a whole bundle of compounds to PoC, wherefrom big pharma can choose those it wants to reclaim and commercialize. An example for a VPC following this business approach is Flexion [18,24], introduced in the previous section. Since it was founded in 2007, the company did not experience difficulties in obtaining sufficient compounds for development. Longman emphasized that large pharmaceutical firms "[...] will have to start thinking of their discovery groups [...] as

[1] The JJDC, Pfizer Venture Funds, Lilly Ventures, SR One of GSK and Novartis Ventures, just to name a few.

[2] For comparison: Between 2000 and 2005, only 5% of Atlas' Life Science deals included corporate venture funds. From 2006-2008, the number increased to 33%.

discovery suppliers to the rest of the biopharmaceutical world" [24]. This equals the open innovation principle of lifting firm boundaries and letting others develop internal assets, which might otherwise not be exploited: 5% of something is more than 100% of nothing. In connection with a shift away from the closed IP model, out licensing could also contribute to increased knowledge sharing and innovation. By providing access to data on neglected diseases, big pharmaceutical companies could further enable VPCs to develop respective medicines – provided they receive adequate funding from alternative sources, such as research councils and NGOs – and thus generate additional benefits for the society.

Managing success factors of collaborations in a complex industry network

Of course, the five modes discussed above represent a simplification of the actual complex and often mixed collaboration structures in industry. Nevertheless, a strategy based on mode 4 – investing – seems to be particularly versatile for big pharma, as it can be combined with or prepare other forms of alliances. Based upon previous investments into VPCs, pharmaceutical companies can gain a foothold for later successful licensing agreements or acquisitions. Moreover, it enables big pharma to influence company decisions and to gain insights on business specifics and on the potential for success of the development targets. The pharma venture investment thereby secures the basic financing of the VPC and due to the cost efficiency of VPCs, the fund can diversify a given investment sum – and thus its risk – on a higher number of companies compared to more traditional investments e.g. in biotech companies. As investor it is further possible to balance the power of other investors, whether they are venture capital or other big pharmaceutical firms. The probability of sudden forced acquisitions and any other negative surprises decreases. However, the issue of knowledge spillovers remains and further, big pharmaceutical companies might be reluctant to invest heavily into companies whose success is critically dependent on the skills of a very small core team.

Still, the factors influencing a partnership are not limited to the mode of collaboration itself. The degree of collaboration, the form of payment and the presence of multiple licensees and

investors are important points to consider as well. To successfully exploit the benefits that collaborations with VPCs offer, pharmaceutical companies must develop a corporate strategy, which embraces the prospects of virtual development and considers its pitfalls. In particular, the mere act of collaborating with a small and flexible VPC does not guarantee an increase in R&D innovativeness and in the number of marketed products [25]: as for any other partnership, pharmaceutical companies should be aware of their objectives, of the associated risks and the required resources. Moreover, relationship planning must exceed the direct operations with the VPC and include post-deal product management. If a pharmaceutical company neglects the latter aspect during a partnership and commercializes the virtually developed product, it might later end up unable to manage the post-launch life cycle and product complaints. The company has therefore to ensure beforehand that sufficient expertise is built up internally. A co-development arrangement with the VPC, for instance, would require active participation of big pharma scientists in the development process, thus acquainting them with the relevant knowledge. Alternatively, the pharmaceutical company could arrange a post-launch agreement with the VPC or acquire the VPC altogether and make the VPC's experienced staff responsible for post-launch activities.

As can be inferred from above, potential big pharma – VPC relationships are numerous and complex. The same, however, is true for any other form of cooperation in the pharmaceutical industry, whether with academia, governments, biotechs, big and small pharmaceutical companies, CROs or CMOs. The various relationships with different partners create a complex cooperation network around a big pharmaceutical company (Figure 3). To successfully navigate within this network, companies need excellent legal and partner management staff. The objectives and scope of each partnership have to be clearly defined and communicated. Risk evaluations and escalation paths need to be in place. Furthermore, a sound cooperation strategy must contain provisions for post-partnership and post-launch operations. It should always be supported by senior management and aligned to the company's overall strategy.

[approximate location of Figure 3]

The combination of several big pharma cooperation networks finally creates an industry network, whose complexity again increases by a multiple. Figure 4 illustrates a simplified version of such a network. These industry networks include several corporate participants such as big pharma, biotechs, CROs, CMOs, VPCs and venture capital firms. Furthermore, academia, regulatory agencies, governments, non-profit organizations and patients are part of the overall network. The collaboration networks of individual pharmaceutical companies, as displayed in Figure 3, interact and overlap. Two fierce competitors might be closely related by their individual partnership structures. The close connections foster a steady flow of expertise and staff within the industry. By installing adequate data bases, duplication of efforts, especially of mistakes, may be reduced if knowledge is shared in a timely manner. It is thus probable that increased collaboration between intra- and extra-sectoral players as well as virtual and open innovation strategies will contribute to creating even closer intertwined and more open business models within the pharmaceutical industry. A necessary prerequisite for this is that pharmaceutical companies develop strategies to tackle the challenges posed by possibly lifting – at least partly – their closed IP business model. Existing programs pointing into this direction, such as the European IMI, which supports collaborative research projects and networks between industry and academia, seem to be very promising [25].

[approximate location of Figure 4]

Concluding remarks

In this article we have presented virtual pharmaceutical companies as a possibility to collaborate flexibly in the pharmaceutical industry. Collaboration in general is practiced by big pharma since many years as a means to tackle the industry's challenges. VPCs can complement today's collaboration networks. They provide established pharmaceutical companies access to a development model that significantly differs from their own. Above, we have defined the concept of virtual companies in the pharmaceutical industry and discussed their main advantages – development speed and efficiency, flexibility and the absence of expensive fixed assets. As VPCs

are not suited to carry out late stage clinical development and commercialization due to the high costs and resource requirements involved, they are very open towards collaboration with large pharmaceutical companies. In the present review we focused on how big pharma can leverage the VPC concept, as so far only anecdotal evidence existed, and we developed five possible modes of collaboration, which often occur as mixtures in practice. We have seen that a strategy based on mode 4 – investing – is particularly versatile for big pharma, as it can be combined with or prepare other forms of alliances. Leveraging the VPC concept offers several advantages for big pharma at modest costs: companies can diversify risks, obtain new inputs for their pipelines and focus on their core competencies and disease areas. When acquiring VPCs, pharmaceutical companies avoid build-up of R&D silos, duplication of efforts and lengthy integration processes, as VPCs only consist of a managerial core. Investments in and exits out of VPCs are therefore easy and clean. Nevertheless, it should be remembered that collaborations with VPCs require a corporate strategy considering the potentials and the risks of VPCs, and that the mere collaboration with a VPC not necessarily leads to an increase in innovativeness and success. Furthermore, particular attention should be attributed to the skill set present in the core team, as it is critical to the performance of a VPC.

Virtual pharmaceutical companies will most likely gain importance in the collaboration landscape of the pharmaceutical industry in the near future. Therefore, further research is needed to obtain more information for instance about the appearance, relative frequency and corresponding success rates of the five collaboration modes presented above or about possible benefits of different types of development projects (orphan drugs, niche indications etc.), which are specific to VPCs or even to single collaboration modes. Furthermore, it would be interesting to study the relationship between the total number of employees or the total investment sum and development efficiency. Together with the study of VPC appearance, pharmaceutical networks could be evaluated and analyzed regarding their openness and their effects on knowledge spillovers.

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Figure Legends

Figure 1: Comparison of business models of virtual and integrated pharmaceutical companies. A virtual pharmaceutical company (VPC) consists only of a small management core holding IP and coordinating external service providers to develop a drug. Integrated pharmaceutical companies, having a large number of own employees and facilities, manage intellectual property (IP), manufacturing, logistics and marketing, and are guided by numerous internal guidelines and standard operating procedures (SOPs). The grey colored parts of the timeline highlight the phases of drug development during which the two types of companies are active. VPCs usually develop their compounds only from pre-clinical until Proof of Concept (PoC), whereas big pharma covers the whole spectrum of drug development. The goal of VPCs is to reach PoC (in red) faster and more cost-efficient than integrated pharmaceutical companies.

Figure 2: Possible modes of cooperation between integrated and virtual pharmaceutical companies (VPCs). The five relationships are in-licensing (1), founding (2), acquiring (3), investing (4) and out-licensing (5). In- and out-licensing may include co-marketing, -promotion and -development. Except for case 2, every VPC owns intellectual property (IP), either from own R&D or from in-licensing. In case 2, the VPC develops compounds of the mother company or of clients in general.

Figure 3: Example of an outsourcing and collaboration network of a pharmaceutical company. Various relationships can be established with multiple corporate partners, including virtual pharmaceutical companies (VPCs), biotechs, other big pharma companies, and contract research and manufacturing organizations (CROs and CMOs). Beside corporate collaboration, a network includes all relationships to regulatory agencies, governments, academia, non-profit organizations, and of course, patients.

Figure 4: A simplified representation of a pharmaceutical industry network. The participants create a complex cooperation network with numerous interactions and overlaps. Examples include co-development partnerships, research joint ventures (RJV) and acquisitions (M&A).

Knowledge flows along the various connections. Networks link companies and investors and allow a joint approach to satisfy patient needs.